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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,077	06/25/2003	Matthew Ashby	ASHBY/1 DIV	1068

1473 7590 07/14/2008

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PATENT DOCKETING 39/361
1211 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8704

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
07/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,077	ASHBY, MATTHEW	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-57* is/are pending in the application.

4a) Of the above claim(s) *51-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-50 and 57* is/are rejected.

7)☒ Claim(s) *57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed April 18, 2008. Claims 45-56 were previously pending, with claims 51-56 withdrawn from consideration. Applicant amended claims 45-49 and added new claim 57. Claims 45-50 and 57 will be examined.

2. Applicant's amendment overcame all of the previously presented rejections. This office action contains new grounds for rejection necessitated by amendment.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on November 15, 2007 was filed after the mailing date of the non-final office action on October 18, 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

4. Claim 57 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 45-50 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 45-50 and 57 are broadly drawn to a culture-independent method of determining the abundance of an environmental parameter of interest by determining the abundance of at least one nucleic acid marker sequence, wherein the abundance of the nucleic acid marker sequence(s) correlates to the abundance of the environmental parameter, comprising the steps of:

a. providing an environmental sample containing a population of interest;

b. isolating genomic DNA from the environmental sample;

c. assaying the genomic DNA by utilizing at least one pair plurality of species-specific probes to at least one of the nucleic acid marker sequences as PCR primers to determine the abundance of at least one of the nucleic acid marker sequences in the genomic DNA isolated from the sample that shows a correlation to the parameter of interest; and

d. inferring the abundance of the parameter of interest based upon the abundance of at least one of the nucleic acid marker sequences in the genomic DNA isolated from the sample.

Claim 46 is drawn to using species-specific probes only, i.e., not as primers. Claim 50 is drawn to the environmental parameter being a subsurface oil or gas field.

However, as will be further discussed, there is no support in the specification and prior art for the methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of how to obtain a correlation between an abundance of a nucleic acid marker sequence and an abundance of any environmental parameter. In Example III on pages 44-46, Applicant examined a diversity of bacteria in two samples taken from Rocky Mountain Oilfield testing center by detecting a number of different 16S rRNA sequence tags in the genomic DNAs extracted from the samples. A total of 58 distinct tags were obtained for the Wy-1 sample, and 79 for the Wy-2 sample. Applicant concluded that 45% of tags obtained from the Wy-1 sample were not present in Wy-2, and 59% of tags present in Wy-2 were not present in Wy-1. There is no further investigation of how the number and/or type of the tags were possibly to be correlated with the presence of any parameter of interest, including oil. Applicant stated the following (page 46, lines 5-9):

"Thus, one cannot conclude that there are tags in these two samples that are indicators for various parameters associated with each sample. Nonetheless, a full-fledged analysis of these samples may provide such indicators."

Further, there are no working examples of detection of any other genetic markers and their correlation with various possible environmental parameters.

Guidance in the Specification

The specification provides no evidence that the disclosed determination of 16S rRNA sequence tags in environmental samples would enable correlation of these tags with any environmental parameters. Further, the specification does not provide any guidance as to the use of

any other genetic markers in correlating an abundance of such marker with an abundance of any environmental parameter. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

The prior art provides a very strong evidence that it is not possible to reliably determine the abundance of different organisms in environmental samples, and, consequently, to correlate such abundance with the environmental parameters of interest. Witzingerode et al. (FEMS Microbiol. Rev., vol. 21, pp. 213-229, 1997; cited in the IDS) examined different stages of sample preparation for the detection of bacterial diversity by PCR amplification of 16S rRNA genes from environmental samples. Their conclusion (page 214, last paragraph):

"However, each physical, chemical and biological step involved in the molecular analysis of an environment is a source of bias which will lead to a distorted view of the 'real world. After 10 years of molecular ecological studies it seems necessary to summarize reported pitfalls of the molecular ecological approach which will most likely lead to an erroneous description of the diversity of a given ecological niche."

In particular, Witzingerode et al. teach that each of the processes leading to and including the PCR amplification step introduces an error in the final number of organisms detected, because of losses of RNA or RNA fragmentation during sample lysis (page 215, last paragraph; page 216, paragraphs 1-3) and introduction of potential polymerase inhibitors (page 216, fourth paragraph) and problems during the PCR amplification process, such as inhibition of amplification by contaminants, non-uniform amplification due to different template properties and formation of PCR

artefacts (page 217-220; page 221, paragraphs 1-5). Finally, since the number of rrn operons varies between different bacterial species and even within a single species the operon sequences vary due to insertion elements, the abundance of different bacterial species cannot be estimated from the abundance of different sequences, since in an unknown sample one does not know the numbers of rrn operons in each bacterial species present. As stated by Witzingerode et al. (page 222, third paragraph):

"In conclusion, 16S rRNA genes of some Bacteria and Archaea reflect the occurrence of inter- and intraspecific *rrn* operon heterogeneities. These differences can interfere with the analysis of 16S rDNA clone libraries or gel electrophoresis patterns derived from environmental ecosystems as it is not clear whether one 16S rDNA sequence represents a distinct organism or is just one representative gene of the entire 16S rRNA operon of an organism. Because it is likely that IVSs are introduced into 16S rRNA genes by lateral transfer their inclusion in phylogenetic analyses can lead to erroneous results."

Colbert et al. (Appl. Env. Microbiol., vol. 59, pp. 2056-2063, 1993) point to a different problem. They examined a relationship between the number of Pseudomonas putida PpG7 in soil amended with salicylate carbon source and the amount of the salicylate added as a function of time (Abstract; page 2057; Fig. 3). They found that increasing the concentration of salicylate initially increased the number of cells in the soil, but the bacterial population remained constant after the salicylate has been consumed (Abstract; Fig. 3D-F; page 2060, last paragraph). Further, high salicylate concentrations lead to the suppression of metabolism and growth of the bacterial cells (Abstract; page 2061, second paragraph). Therefore, in case of bacterial species which depend on certain substances for growth, once the substances are exhausted their populations might not

decrease, making the correlation between the presence of such substance and the number of bacteria impossible.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to detection of any number of environmental parameters with any type of nucleic acid marker, which includes not only bacterial nucleic acid markers but any nucleic acid marker which can be found in the sample. Such parameters include choice of a number of different nucleic acid markers and testing those markers to determine whether the amount obtained by PCR or probe hybridization correlates with the presence of an oil deposit in the soil, for example. As the possible number of environmental parametrs is practically infinite, and the number of potential markers to study in the millions, this would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the abundance of a certain nucleic acid marker as detected by PCR or hybridization depends upon numerous known and unknown parameters such as the method of RNA extraction, type of organisms present in the sample, time in which the sample was collected, etc., the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the rRNA sequences for the determination of bacterial diversity. Thus given the broad claims in an art whose nature is identified

as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Interpretation

7. The term "environmental sample" has not been defined by Applicant, therefore it is interpreted as any sample.

8. The term "environmental parameter of interest" has not been defined by Applicant, therefore it is interpreted as any parameter.

9. The term "parameter of interest is surface oil or natural gas deposit" in interpreted as any parameter pertaining to oil or gas.

10. The terms "perfect correlation", a "high degree of correlation" and "moderate degree of correlation" have not been defined, therefore, the first two terms are treated as equivalent, and the third as any degree of correlation.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 45-49 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Wikstrom et al. (J. Biotechnol., vol. 52, pp. 107-120, 1996).

Claims 45 and 46 are considered together in claim 45, since it is a species of claim 46.

Regarding claims 45 and 46, Wikstrom et al. teach a culture-independent method of determining the abundance of polycyclic aromatic hydrocarbons (PAHs) (=an environmental parameter of interest) by determining the abundance of an active catechol 2,3-dioxygenae gene (=at least one nucleic acid marker sequence), wherein the abundance of the nucleic acid marker sequence(s) correlates to the abundance of the environmental parameter, comprising the steps of:

a. providing an environmental sample containing a population of interest (page 108, last two paragraphs; page 109, first paragraph; page 111);

b. isolating genomic DNA from the environmental sample (page 109, last paragraph; page 110, paragraphs 1-5);

c. assaying the genomic DNA by utilizing at least one pair plurality of species-specific probes to at least one of the nucleic acid marker sequences as PCR primers to determine the abundance of at least one of the nucleic acid marker sequences in the genomic DNA isolated from the sample that shows a correlation to the parameter of interest (page 110, last two paragraphs; page 112, first and second paragraphs; page 113 and Table 3; page 114; page 116, first paragraph; page 117, first paragraph); and

d. inferring the abundance of the parameter of interest based upon the abundance of at least one of the nucleic acid marker sequences in the genomic DNA isolated from the sample (page 117, first paragraph; Table 7; page 119, fourth paragraph).

Regarding claims 47-49, Wikstrom et al. teach a perfect correlation between the abundance of the catechol 2,3-dioxygenase DNA and the PAH concentration in the sample (Table 7).

Regarding claim 57, Wikstrom et al. teach choosing the gene on the basis of its function in using PAHs as substrates (page 108, second and third paragraph; page 119, paragraphs 2-4).

13. No claims are allowed.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 6, 2008